

REMARKS

Reconsideration is requested.

The claims have been amended to define the elected subject matter.

The Examiner is requested to appreciate that claim 1, and claims dependent therefrom, define methods. Claims 1-31 are indicated in the Office Action of August 23, 2007 and above as having been withdrawn however the Office Action of March 26, 2007 fails to identify the claimed methods as being separately patentable. The Examiner is requested to either indicate that claims 1-30, which define methods, are rejoined and examined (claims 5, 10 and 30 have been canceled above as not reciting the elected compound), or specifically indicate that the subject matter of the claimed methods 1-30 define a separately patentable Group to which the applicants may file a separate divisional application.

Withdrawn composition claim 31 has been revised above to be dependent from compound claim 34. Rejoinder and consideration of claim 31 with the remaining product claims is requested.

Rejoinder and allowance of any claim defining a method of making and/or using a product defined by an allowable claim, at an appropriate time, are requested.

The Section 112, second paragraph, rejection of claim 1 is traversed.

Reconsideration and withdrawal of the rejection are requested in view of the following.

Initially, the applicants note that claim 1 has been withdrawn from consideration, and claim 1 does not recite the objected-to term (i.e., "solvate").

In the interest of advancing prosecution, the applicants presume the Examiner meant to reject claim 34 for the recitation of “solvate”. Clarification is requested in the event the applicants presumption in this regard is incorrect and another unstated rejection was intended.

Solvates are defined and described in the specification, or example, as a complex of the compound of formula I (or a salt thereof) and a solvent (see page 31, line 28 *et seq.*). Compounds are regularly defined in U.S. Patent claims as including solvates, which will be understood by those of ordinary skill in the art. A quick search of the U.S. Patent Office on-line database indicates that 3918 patents have issued since 1976 wherein the objected-to term is included in the claims. While the applicants have not reviewed the patents revealed in the search, the number of issued patents containing the objected-to term is believed to be persuasive evidence that the ordinarily skilled artisan is familiar with the term.

Withdrawal of the Section 112, second paragraph, rejection of claim 1 is requested.

The Section 112, first paragraph “enablement”, rejection of claims 34-50 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Initially, the applicants note that to be to be enabling under §112, a patent application must contain a description that enables one skilled in the art to make and use the claimed invention. Raytheon Co. v. Roper Corp., 220 USPQ 592 at 599 (Fed. Cir. 1983). That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive. See, e.g., W.L.

Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303, 316 (Fed.Cir. 1983), cert. denied, 53 U.S.L.W. 3226 (U.S. Oct. 2, 1984); In re Angstadt, 190 USPQ 214, 218 (CCPA 1976).

Moreover, in chemical cases, the sheer number of compounds covered or defined by the claims is not dispositive as to the enabling issue. See Atlas Powder Company v. E.I. Du Pont De Nemours & Company, 224 USPQ 409 (Fed. Cir. 1984) (claim that covered thousands of compounds satisfied section 112's enabling requirement).

Specifically, Du Pont argued in Atlas that the patent disclosure at issue listed numerous salts, fuels, and emulsifiers that could form thousands of emulsions but that there was no commensurate teaching as to which combination would work. The disclosure, according to Du Pont, was nothing more than "a list of candidate ingredients" from which one skilled in the art would have to select and experiment unduly to find an operable emulsion.

The Federal Circuit rejected the arguments of Du Pont in Atlas and found the claims at issue to be supported by an enabling disclosure. The Atlas Court concluded that even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. Specifically, the Court noted that "It is not a function of the claims to specifically exclude * * * possible inoperative substances * * *", citing to In re Dinh-Nguyen, 181 USPQ 46, 48 (CCPA 1974) and In re Geerdes, 180 USPQ 789, 793 (CCPA 1974), and In re Anderson, 176 USPQ 331, 334-35 (CCPA 1973).

The presently claimed invention is supported by an enabling disclosure, as was described by the Atlas Court, for example. Consideration of the following in this regard is requested.

Throughout the Office Action of August 23, 2007, the examiner is understood to believe that the amount of experimental burden placed on the skilled person is undue. In each instance the examiner has not referred however to any specific problem identified in the art that would require the ordinarily skilled person to exercise an undue burden to prepare the compounds of the claimed invention. A few general concerns are believed to be expressed by the examiner, but these are not concerns that would have troubled the ordinarily skilled person wishing to make and use the claimed invention, to the extent that burdensome experimental studies would have been required to overcome those concerns.

The Breadth of the Claims

As noted above by the Atlas Court, the mere breadth of the claims does not necessarily require a conclusion that undue experimentation would be required to make and use the claimed invention. The examiner is to be reminded that many compound claims are granted where the claims cover a seemingly endless possibility of compound structures. This, in itself, is not a barrier to patentability.

The Level of Skill in the Art

The applicants submit, with due respect, that it is a misjudgement of the examiner to rely on the 'unpredictability in the art of organic synthesis' in rejecting the claims for an alleged lack of enablement. In fact, organic synthesis relies on the predictable and reproducible nature of a wide range of chemical transformations.

Otherwise, organic synthesis would be highly cumbersome - the skilled person would need to investigate the reliability of a particular reagent for every similar transformation. This is clearly not the case. Unless the art specifically teaches otherwise, the ordinarily skilled person will approach a synthesis with a mind that is willing to apply the known to a new compound, with a rational and scientific expectation of success.

To assess each embodiment of the invention individually for viability is therefore artificial and fails to appreciate the generally advanced level of skill in the art of organic synthesis. The embodiments can be assessed together, taking into account the common structural elements, as the ordinarily skilled person would undoubtedly have done at the time of the invention.

The Amount of Direction or Guidance Present

The examiner is understood to dismiss the compounds that he believes fall outside the scope of the elected group. The sections of text relating to these compounds however discusses chemical transformations that may be performed successfully on starting materials having high structural similarity to the compounds of the elected group.

It is worth noting that the present invention does not provide a core chemical structure that would be viewed by the ordinarily skilled person as being highly complex. The claimed invention requires inclusion or addition of functional groups to this core structure in a manner which commonplace in organic synthesis. There is nothing in the art to suggest that the sulfur-containing compounds of the invention, for example, are difficult to prepare or would require more than routine experimentation. The examiner is requested to see, for example, the compounds in table 4, which were commercially

available at the time of filing. The similarity of the central portion of these compounds to the structures of the present invention, show that the methodologies required by the present application were well within the scope of the ordinarily skilled person.

The examiner is understood to assert that the specific examples of the application are limited to the compounds of formula I wherein $R^1 = H$; $L^3 = \text{single bond}$; $R^3 = H$, $L^4 = CH_2$, $R^4 = H$. The examiner is further understood to believe this to be an 'extremely limited' selection. The Examiner's conclusions however do not recognize the degree to which the examples of the application are generally applicable to the claims.

For example, it will have been readily apparent to one of ordinary skill in the art that compounds where the identities of the groups L^4 and R^3 are swapped with those of L^3 and R^2 may be readily prepared from the alternative 3-mercaptobenzyl alcohol starting material. The ordinarily skilled person will understand that these examples represent a teaching that is boarder than that believed to be proposed by the examiner.

The applicants further note that the description makes reference to Vogel's *Textbook of Practical Organic Chemistry* (see page 28, lines 12-17) which provides a wide ranging selection of chemical functional group transformations.

The present application does not provide a comprehensive list of possible starting materials for use in the synthesis of the compounds of the invention. After all, the choice of starting material is dependent on the nature of the intended product and also the intended synthetic route. Indeed many different starting materials may be available for a particular product and an understanding of same will be within the skill of the artisan.

Simple mercapto compounds for use in the preparation of compounds of the invention, for example, are available commercially. Compounds such as mercaptobenzoic acid, mercaptobenzyl alcohol, mercaptophenol, mercaptophenylacetic acid, methyl thiosalicylate and aminothiophenol can be obtained from Sigma Aldrich for example, along with various halogenated thiophenols as well. The transformation of these compounds into compounds of the invention may be realized by the ordinarily skilled person, using the teachings of the present application and the common general knowledge, without undue experimentation.

The preparation of more complex compounds may be achieved using any one of the simpler starting materials described above. Alternatively, more complex compounds may be purchased commercially, and transformed into compounds of the present invention. The compounds listed in table 4 of the application, for example, could be modified in this way.

The compounds in table 4 can be prepared as described in scheme 2 togetherwith the references cited on page 39. A review on the synthesis of hydroxamic acids can be found in: Yang, Kexin; Lou, Boliang. **Molecular diversity of hydroxamic acids : Part I. Solution- and solid-phase synthesis.** Mini-Reviews in Medicinal Chemistry (2003), 3(4), 349-360.

The compounds of the invention contain a hydroxyamide group (-C(O)N(OH)-). The examiner is understood to note that the application describes only one method for introducing this functionality. As is clear from the description and the examples, a hydroxylamide group may be derived from a corresponding hydroxylamine. As the examples show, the hydroxyamine functionality may be introduced into a molecule of

interest by nucleophilic substitution of a halogen at a benzylic carbon. This is one example however there are many more known in the art.

For example, Kalsi *et al* (*Journal of Medicinal Chemistry* **2000**, 43, 3981) shows an alternative approach to introducing a hydroxylamide functionality into a molecule (see Scheme 1). The approach involves activating a hydroxylamine with chloroformate. This activated form may then be reacted with an appropriate nucleophile to introduce the required -C(=O)N(OH)- functionality into the product molecule.

The State and Predictability of the Art

The examiner is understood to have raised an issue regarding regioselectivity with regard to product compounds having thiol functionality. Particularly, the examiner has argued that a differential protecting group strategy is needed in order to prepare a compound of the invention including -L¹-COOR⁶ and multiple thiol (-SH) functionality. The examiner has argued that to establish a strategy would place an undue burden on the skilled person.

The examiner's arguments in this regard are, at best, of a general nature, and make no reference to any real problem or prejudice in the art associated with the synthesis of compounds having thiol and thioether functionality.

In the exemplified syntheses, a preferred intermediate is a substituted thiophenol compound (see scheme). The thiol group is reacted with an α -bromo ketone to introduce the group that will be -L¹-COOR⁶ in the final product. The examiner questions how a product where R³ has a thiol substituent could be prepared. The examiner is understood to be concerned that if R³ of the intermediate has a thiol substituent then it

has the potential to react with the ketone. This, according to the examiner, 'demands' a differential protecting group strategy.

The use of protecting group chemistry is well established in organic synthesis to the extent that it is entirely routine. The selection of a particular protecting group for a particular reactive moiety is believed to be routine for the ordinarily skilled synthetic chemist. Owing to the ubiquitous nature of protecting group chemistry, the ordinarily skilled person will have experience in working with and selecting protecting groups for a particular purposes. Textbooks like Greene and Wuts and alternatives such as Kocienski's *Protecting Groups* (Thieme, Stuttgart, 2000), show how protecting groups can be used predictably in a wide range of chemical transformations.

The ordinarily skilled person would not share the examiner's concerns about thiol protecting group strategy. Firstly, differential protecting group strategies are available for thiol groups. These are well documented in Greene and Wuts. An entire chapter is devoted to thiol protection – see chapter 6, page 454 onwards of the third edition. The data contained within table 7 (see page 732 onwards) also show the reactivity of each of the protecting groups, and on this basis protecting groups having differential reactivities may be selected. Thus, there is no undue burden on the ordinarily skilled person to select and utilize a protecting group strategy for the thiol group.

Secondly, there is no need for there to be a thiol group at this particular stage of the synthesis. Instead, the thiol group could be 'masked' as a hydroxyl group (protected or otherwise) which is to be later converted to a thiol. Thus, the hydroxyl group represents latent thiol functionality. Such functional group interconversions are entirely commonplace in organic chemistry. One well known example is the conversion of a

hydroxyl group to a bromide using NBS and PPh_3 . Such a conversion is shown in Gribble *et al* (*Biochem. Pharmacol.* **1996**, 53, 1227 – see chart 3, method A).

Furthermore, the presence of another free thiol group in an intermediate compound is not something that need be avoided for a chemoselective approach to functionalisation may allow one thiol group to be reacted in preference to another. The reactivity of an R^3 thiol functionality may differ significantly from that of the thiol substituent on the aromatic ring. The judicious use of molar equivalents of base and/or reagent can ensure that only one of these groups reacts. Such reactivity can be the basis for differentially protecting thiols in an intermediate compound, or for introducing the group that will be $-\text{L}^1-\text{COOR}^6$ in the final product.

The examiner argues that the application does nothing to alley the 'unpredictable limitations of the art of organic chemistry with respect to sulfur containing molecules'. An example presented by the examiner is a hydrogenation reaction in which the metal catalyst is poisoned (it is alleged) by a sulfur containing starting material.

The use of hydrogenation chemistry is nowhere suggested in the application. Perhaps the examiner is concerned about the use of benzylic protecting groups and the like in the synthesis of compounds of the invention. However, the use of such groups can be easily avoided by appropriate planning. For example, a reliable alternative to a benzylic ether would be a silyl ether protecting group.

In any event, hydrogenation over a metal catalyst is not the only way of reducing a particular functionality and many other reaction conditions can be used instead. For example, a benzyl ether protecting group could be removed using the conditions listed in Greene and Wuts, pages 79-98.

The examiner's concerns above relate to points that would have been dealt with by the ordinarily skilled person as a matter of routine during the planning of and preparation for a compound synthesis, with reasonable experimentation.

The examiner has discussed a number of points in relation to the Suzuki coupling reaction shown in scheme 5. The Suzuki reaction is typically a reaction of an aryl boronic acid (or ester) with an aryl halide (although vinyl esters and halides may also be used in place of the aryl groups). The examiner again argues that regioselectivity is an issue here. If the aryl halide has multiple halide substituents, the examiner suggests that the product of the reaction is unpredictable. The Examiner is understood to argue that an undue burden would be required to control the regioselectivity.

The applicants response to these points raised by the examiner are similar to the comments set out in relation to thiol selectivity. First of all, although the final product may have a halogen atom at a certain ring position (such as R¹), that is not to say that this particular substituent was or need be present in the intermediate that is utilised in the Suzuki coupling reaction. Another functional group may be at this position instead. Later, this group may be converted to the appropriate halogen using standard functional group transformations. Alternatively, the ring may be unsubstituted at this point, and subsequent to the coupling reaction, the halogen substituent is then added.

The examiner is to be reminded, with due respect, that the coupling partners may be reversed. Thus the molecule shown as an aryl boronic acid may be used instead as an aryl halide, and the aryl halide may be used as an aryl boronic acid. The use of an excess of aryl halide can reduce the amount of self-coupling where the aryl boronic acid also includes halide functionality.

The Suzuki reaction is presented as one example of a metal catalysed insertion reaction. Many other reactions are known, including the Stille, Heck and Sonagashira reactions. These types are well known to the ordinarily skilled chemist, and the factors that influence the reactivity of the insertion partners has been well studied.

The alleged problems presented by the examiner could be solved by the ordinarily skilled person without undue burden. For each of the scenarios, there are many solutions, and each of these is well known, and well used in the art.

The Quantity of Experimentation Needed

The examiner is understood to believe that there is a substantial gap between the guidance provided in the description and the breadth of the claims.

The examiner has noted that compound E is inactive in the cell proliferation assay. Nevertheless, the ordinarily skilled person will have noted that the compound still has the ability to inhibit glyoxalase I. The ordinarily skilled person is therefore fully entitled to take from this result the knowledge that this type of compound has inhibitory activity against a protein that is implicated in cancer.

In view of all of the above, the applicants submit that the claims are supported by an enabling disclosure and that undue experimentation would not be required to make and use the claimed invention.

Withdrawal of the Section 112, first paragraph, rejection of the claims is requested.

A response to the Requests filed September 13, 2007 is again requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably

ASHTON et al.
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Amendment

by telephone, in the event anything further is required to place the application in
condition for allowance.

Respectfully submitted,

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